Potential of dihydropyrimidine dehydrogenase genotypes in personalizing 5-fluorouracil therapy among colorectal cancer patients

Abstract

BACKGROUND: Dihydropyrimidine dehydrogenase (DPD) is a pyrimidine catabolic enzyme involved in the initial and rate-limiting step of the catabolic pathway of toxic metabolites of 5-fluorouracil (5-FU). Several studies have reported that deficiency of DPD and polymorphisms of its gene are related to 5-FU toxicities and death. Association between serum concentration of 5-FU and its related toxicity has also been previously demonstrated. Hence, this study aims to understand the role of DPYD variants in serum level of 5-FU and the risk of developing toxicity to prevent adverse reactions and maximize therapy outcome for personalized medicine. METHODS: A total of 26 patients comprising 3 different ethnic groups (Malay, Chinese, and Indian) diagnosed with colorectal cancer and treated with 5-FU chemotherapy regimen from local hospital were recruited. Polymerase chain reaction and denaturing high-performance liquid chromatography methods were developed to screen polymorphisms of DPYD gene. High-performance liquid chromatography-based quantification assay was developed to measure the serum concentration of 5-FU among these patients. RESULTS: Patients with DPYD genotypes of deficient enzyme activity had higher median serum levels of 5-FU compared with normal DPD group (median, 11.51 mcg/mL; 95% confidence interval, 10.18-16.11 versus median, 0.83 mcg/mL; 95% confidence interval, 0.55-5.90, Mann-Whitney U test; P = 0.010). Patients with neutropenia (n = 11) had significantly higher serum concentrations of 5-FU as compared with those with normal white blood cell count (n = 15) (Mann-Whitney U test, P = 0.031). Combined regression analysis showed that the predictive power of DPYD*5 (rs1801159) and 1896 T>C (rs17376848) for serum concentrations of 5-FU in the studied group was 36.6% (P = 0.04). Similarly, DPYD*5 and 1896 T>C accounted for 29.9% of the occurrences of neutropenia (analysis of variance, P = 0.017). CONCLUSIONS: This study revealed that DPYD*5 (rs1801159) and 1896 T>C (rs17376848) are potentially useful predictive markers of patients' responses to 5-FU chemotherapy. Pharmacogenotyping is therefore recommended to guide dosing of 5-FU and prevent neutropenia.

Keyword: 5-fluorouracil; Dihydropyrimidine dehydrogenase; Pharmacogenotypes; Adverse effect; Neutropenia